REMARKS

Claim Status

Claims 1-6 and 11-29 are cancelled. Claims 7-10 were previously withdrawn. Claims 30-46 are newly added. This listing of claims will replace all prior versions, and listings of claims, in the application.

Claims 30-46 have been rewritten as new claims for the purpose of clarity. Claim 30 corresponds to original claims 4 and 11. Claim 31 corresponds to original claim 12. Claim 32 corresponds to original claim 5. Claim 33 corresponds to original claim 6. Claim 34 corresponds to original claim 14. Claim 35 corresponds to original claim 15. Claim 36 corresponds to original claim 16. Claim 37 corresponds to original claim 17. Claim 38 corresponds to original claim 18. Claim 39 corresponds to original claim 19. Claim 40 corresponds to original claim 22. Claim 41 corresponds to original claim 23. Claim 42 corresponds to original claim 24. Claim 43 corresponds to original claim 25. Claim 44 corresponds to original claim 27. Claim 45 corresponds to original claim 28. Claim 46 corresponds to original claim 29. Support for the amendments can be found throughout the specification and claims as originally filed.

The amendments do not constitute an admission that the previously pending claims were anticipated, obvious, non-enabled, inadequately described or indefinite. Applicants reserve the right to file cancelled subject matter in a continuation or divisional application. Applicants respectfully request reconsideration of the claims in light of the following arguments. Applicant believes that the Application is in a condition for allowance.

I. Summary of the Inventions

The claimed invention is a pharmaceutical ***composition*** comprising 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone and a pharmaceutically-acceptable excipient.

The specification as filed establishes that this compound has utility in treating "various fibrosis diseases and inflammations leading to fibrosis, for example, the fibrosis or fibrous tumor of the tissues such as cardiac muscle, liver, lung, kidney, blood vessel and skin. Exemplary examples include, but not limited to, liver fibrosis, cirrhosis, liver necrosis, chronic obstructive pulmonary disease, lung fibrosis, cardiac muscle fibrosis, kidney fibrosis, blood vessel fibrosis, skin scar, etc."

See [0045] of the published specification – US 2007-0049624 A1). Applicants will likely pursue claims directed to a method of treatment in a divisional application.

II. Summary of the References Discussed in This Response

EP Patent App. No. 0 702 551 is a patent application filed by Solomon Margolin (hereinafter, "Margolin 2"). Margolin 2 is a national phase entry of WO 94/26249, which has an international filing date of May 9, 1994. WO 94/26249 claims priority to US App. No. 08/059,214, filed May 1993, and US App. No. 08/064,831, filed May 1993.

US Patent No. 6,090,822 (hereinafter, "Margolin 1") has been cited by the Office against the current claims. Solomon Margolin is also the inventor of this filing. Margolin 1 corresponds to US App. No. 09/162,011, which was filed in 1998. Margolin 1 is a CiP of US App. No. 08/913,202, which was filed in 1997.

Margolin 2 is not directly related to nor does it share priority with Margolin 1.

III. The Prior Art As A Whole Teaches Away from A Composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone

Per MPEP 2145(X)(D), "the prior art must be considered in its **entirety**, including disclosures that teach away from the claims." Thus, the prosecution history of Margolin 2 must be considered as part of the prior art.

During prosecution of Margolin 2, data was submitted that showed that 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone had a relative anti-fibrotic activity of 0.0, that is **no anti-fibrotic activity at all** (i.e., it was not therapeutically effective).

- One of ordinary skill in the art would not be motivated to invent a pharmaceutical composition comprising 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone when the prior art (i.e., the prosecution history of Margolin 2) teaches that the compound has no demonstrable activity (i.e., it was not therapeutically-effective). Thus, a pharmaceutical composition comprising a compound having no demonstrable activity is non-obvious. Further, the Office should consider that the phrase "a therapeutically-effective amount" is a limitation of the

claim and that the prior art teaches that there is no "therapeutically-effective amount" of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone.

Further, per MPEP 2145(X)(D)(3) "the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of non-obviousness.

- During prosecution of Margolin 2 data was submitted that showed that 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone had a relative anti-fibrotic activity of 0.0, that is **no anti-fibrotic activity at all**.
- Applicants assert the disclosures during the prosecution of Margolin 2 established accepted wisdom that 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone has no anti-fibrotic activity.
- Applicants have proceeded contrary to accepted wisdom in formulating a composition comprising a compound with no anti-fibrotic activity (i.e., no "therapeutically-effective amount"). Thus, the use of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone in pharmaceutical composition is non-obvious.

IV. 5-methyl-1-(4'-methoxyphenyl)-2-(1H)-pyridone Is Irrelevant

The Office states that "compound 5-methyl-1-(4'-methoxyphenyl)-2-(1H)-pyridone taught by Margolin 1 is structurally similar to the instantly claimed compound except for the methoxy substitution on the phenyl ring instead of the hydroxy...substitution of the instantly claimed compound."

This argument is irrelevant in light of the teachings of Margolin 2. It does not matter whether substituting a hydroxy for a methoxy is obvious (Applicants do not concede that such a substitution would be obvious – see section (IV)).

- One of skill in the art would not make the substitution because one of skill in the art would know (from the prosecution history of Margolin 2) that 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone has no demonstrable activity (i.e., no "therapeutically-effective amount").

V. Obviousness Based on Chemical Structure Is Not Applicable

Case law sets out the requirements for finding obviousness based on chemical structure. The Office is clearly ignoring these requirements in its analysis.

First, "the reference compound [must be] so closely related to the claimed compound that a chemist would find the difference an obvious variation." (*See* In re Bluestone, 135 USPQ 199, 200). Substituting a hydrogen for a methyl can be (but, is not always) an obvious variation (e.g., phenyl vs. 2-methyl phenyl). However, changing an ether (-OCH_3) to an alcohol (-OH) would significantly change the chemical properties of the compound and thus, would not be an obvious variation.

- An alcohol is acidic; an ether is not.
- An alcohol is very polar; an ether is only slightly polar.

A chemist would not think of an alcohol and an ether as obvious variants absent some secondary teaching of equivalence. Even the PTO recognizes that alcohols and ethers are patentably distinct - the PTO has separate classifications for alcohols (Class/subclass 568/700-923) and ethers (Class/subclass 568/579-699).

Second, there must be an "expectation that compounds of similar structure will have similar properties." (*See* In re Payne, 606 F.2d 303, 313). A chemist would not think that substituting an ether with an alcohol would produce compounds with similar properties. The acidity and polarity of the compounds would be different; therefore, one would reasonably expect that the properties would also be different. Further, while the hydrogen in an alcohol readily disassociates from the oxygen, the methyl in an ether does not readily disassociate from the oxygen. Thus, in one situation the oxygen is available for a reaction; in the other situation, the oxygen is generally inaccessible.

The Office cites *In re Henze* as supporting its position. However, *In re Henze* was limited to homologues that differed from each other by a CH_2. Per *In re Henze*, "the nature of homologues and the close relationship the physical and chemical properties of one member of a series bears to **adjacent** members is such that a presumption of unpatentability arises against a claim directed to a composition of matter, the adjacent homologue of which is old in the art." The current compound and 5-methyl-1-(4'-methoxyphenyl)-2-(1H)-pyridone are not homologues nor are they adjacent members of a series of compounds. Thus, *In re Henze* does not support the Office's position.

The Office also cites *In re Wood* as supporting its position. However, *In re Wood* is also limited to adjacent members of a series of compounds and thus is not applicable to an analysis of the current compounds. *In re Wood* dealt with an application claiming disubstituted compounds (i.e., 2-amino-4-hydroxy-7,7-dimethyl-7,8-dihydropteridine-6-carboxaldehyde and 2-amino-4-hydroxy-7,7-diethyl-7,8-dihydropteridine-6-carboxaldehyde). The prior art taught compounds that only differed

from the *Woods* compounds in that the prior art compounds were unsubstituted at the 7,7-positions. Thus, *In re Wood* does not support the Office's position.

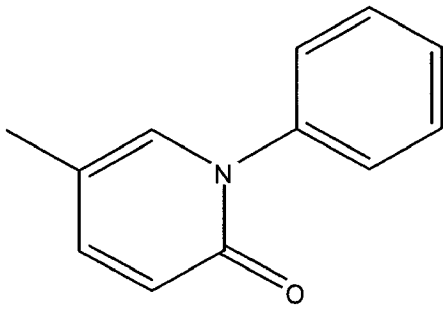
In Office next cites *In re Lohr* as supporting its position. However, *In re Lohr* is also limited to adjacent members of a series of compounds and thus is not applicable to an analysis of the current compounds. *In re Lohr* dealt with compounds that only differed from the prior art due to the presence of two methyls (dimethylthioxanedithiol S,S-bis(O, O-diethylphosphorodithioate) versus 2,3-thioxanedithiol S,S-bis(O, O-diakylphosphorodithioate)). Thus, *In re Lohr* does not support the Office's position.

Finally, the Office cites *Ex Parte Bluestone* as supporting its position. Bluestone involved compounds that differed by a bond (a secondary amine vs. a tertiary amine). While not technically homologues, these compounds were found to be "so closely related that a chemist would find the difference an obvious variation." The Court further stated that "chemists are well aware of the difference between secondary and tertiary amines and their reactivities". However, neither of these holdings are applicable to compounds that differ due to the presence of an alcohol versus an ether. Finally, *Ex Parte Bluestone* also stated that "the variation involved is not seen to be of such character as would lead to any signification modification of fungicidal activity." Again, it is clear to any chemist that substituting an alcohol for an ether is the sort of variation that would lead to a change in biological activity. Thus, *Ex Parte Bluestone* does not support the Office's position.

VI. Unexpected Properties

Case law also sets forth evidence that rebuts a finding of obviousness based on chemical structure. "[An] [u]nexpected property possessed by [a] compound would be evidence of its unobviousness" (In re Wood 199 USPQ 137).

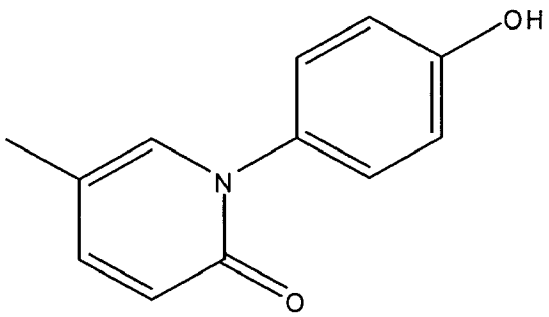
The prosecution history for Margolin 2 demonstrated that "even minor structural changes from that of pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) can significantly affect the properties..." (*see* Response dated October 1, 1999).



5-methyl-1-phenyl-2-(1H)-pyridone

"Pirfenidone"

Per the prosecution history of Margolin 2, substitution on the phenyl ring of N-phenyl 2-(1H)-pyridone compounds provides compounds that have **NO** antifibrotic activity. 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) comprises a hydroxy substitution on the phenyl ring.



5-methyl-1-(4'-hydroxyphenyl)-2-(1H)-pyridone

Unexpectedly and contrary to accepted wisdom (established by the prosecution history of Margolin 2), 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone demonstrates greater anti-fibrotic activity than pirfenidone (*See* Exhibit A). Therefore, a pharmaceutical composition of a 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) is not obvious.

VII. The Office Has Not Met Its Prima Facie Burden

Per MPEP 2142, "the examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness." Further, MPEP 2142 states that "the key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR International Co. v. Teleflex Inc.,... noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit."

- The Office has not explicitly explained why one of skill in the art would make a pharmaceutical composition using a compound with no demonstrable activity. Without such an explicit showing, the Office has not met its prima facie burden.
- The Office has not explicitly explained why one of skill in the art would substitute an ether with an alcohol. Without such an explicit showing, the Office has not met its prima facie burden.

VIII. Response to the Office's Arguments

In the Final Office Action dated May 12, 2009, the Office states that "Margolin [1] actually teaches a pharmaceutical composition of the instantly claimed drug and motivates an ordinary skilled artisan to further test the composition." Because this theory does not take into account the "prior art as a whole" this theory is an erroneous basis for finding obviousness.

In the Final Office Action dated May 12, 2009, the Office states that "there are several methods to assay for anti-fibrotic activity and the fact that the instantly claimed drug does not demonstrate any activity in that particular assay tested by Margolin [1], will not teach away an ordinary skilled artisan from the use of the compound."

- As disclosed in MPEP 2142, "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some **rational underpinning** to support the legal conclusion of obviousness."
- The Office has provided no evidence that the "several methods to assay for anti-fibrotic activity" known at the time this invention was made would produce completely (not, partially) divergent results (i.e., one assay indicates absolutely no activity and the second assay indicates activity).
- Without such evidence, the Office is merely guessing that one of skill in the art would ignore the results disclosed in the prosecution of Margolin 2. The Office has not provided the required rational underpinning.

CONCLUSION

Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 232415 (Attorney Docket No. 34569-716.831).

Respectfully submitted,

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Date: May 13, 2010

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